

LISTING OF CLAIMS

1. *(currently amended)*: A method for making ~~obtaining~~ a prognosis in a subject of
(i) enhanced recovery from an inflammatory condition, [[for]] a subject having, or
(ii) increased at risk of developing, the [[an]] inflammatory condition,
the method comprising determining a genotype defined by ~~of said subject at a~~ one or
more polymorphic sites in the ~~subject's~~ toll-like receptor 2 (TLR-2) nucleic acid sequence
in the subject sequence,
wherein said genotype is (a) a protective genotype that is predictive or indicative of an enhanced
ability of the subject to recover from the inflammatory condition, or (b) a risk genotype that is
predictive or indicative of said increased risk for developing the inflammatory condition.
2. *(currently amended)*: The method of claim 1, wherein the one or more polymorphic sites
includes ~~is at~~ position 201 of SEQ ID NO: 1 or [[at]] a polymorphic site in linkage disequilibrium
~~thereto~~ therewith.
3. *(currently amended)*: The method of claim 1 ~~any one of claims 1-2~~, further comprising
comparing the determined genotype ~~so determined with known~~ genotypes that ~~which~~ are known
to be prognostic ~~indicative of a prognosis for recovery from:~~ (i) the subject's type of an
inflammatory condition; or (ii) another inflammatory condition.
4. *(currently amended)*: The method of claim 1 ~~any one of claims 1-3~~, further comprising
ascertaining ~~determining~~ the TLR-2 sequence ~~information for~~ of the subject.
5. *(currently amended)*: The method of claim 1 ~~any one of claims 1-4~~, wherein said
~~determining of genotype~~ determination is performed on a nucleic acid sample from the subject.
6. *(currently amended)*: The method of claim 5, further comprising the step of obtaining the
[[a]] nucleic acid sample from the subject patient.
7. *(currently amended)*: The method of claim 1 ~~any one of claims 1-6~~, wherein said
~~determining of genotype~~ is determined by ~~comprises~~ one or more of the following methods:
 - (a) restriction fragment length analysis;
 - (b) sequencing;
 - (c) hybridization;
 - (d) oligonucleotide ligation assay;
 - (e) ligation rolling circle amplification;

- (f) 5' nuclease assay;
- (g) polymerase proofreading methods;
- (h) allele specific PCR; and
- (i) reading sequence data.

8. *(currently amended)*: The method of claim 1 ~~any one of claims 1-7~~, wherein the risk genotype of the subject is predictive or indicative of (a) decreased likelihood of recovery from [[an]] the inflammatory condition or [[an]] (b) increased risk of having a poor outcome from the inflammatory condition.

9. *(currently amended)*: The method of claim 8, wherein the subject is critically ill and the presence of the risk genotype is predictive or indicative of a prognosis of severe cardiovascular or respiratory dysfunction.

10. *(currently amended)*: The method of claim 8 [[or 9]], wherein the risk genotype comprises at least one T nucleotide at position 201 of SEQ ID NO:1.

CANCEL Claim 11

12. *(currently amended)*: The method of claim 1 [[11]], wherein the subject is critically ill and the protective genotype is predictive or indicative of a prognosis of less severe cardiovascular or respiratory dysfunction.

13. *(currently amended)*: The method of claim 1 ~~11 or 12~~, wherein the protective genotype is defined as homozygosity homozygous for the A nucleotide at position 201 of SEQ ID NO: 1.

14. *(currently amended)*: The method of claim 1 ~~any one of claims 1-13~~, wherein the inflammatory condition is one that is due to, or associated with, selected from the group consisting of: Gram-positive, Gram-negative, culture-negative or fungal sepsis; septicemia; [[,]] septic shock; fever; bacterial viral, fungal or parasitic infection including Group A streptococcus infection; inflammation due to trauma, surgery or a medical or surgical condition associated with increased risk of infection or sepsis; [[,]] pneumonia; [[,]] ~~septic shock~~, systemic inflammatory response syndrome (SIRS); [[,]] Acute Respiratory Distress Syndrome (ARDS); [[,]] acute lung injury; [[,]] infection, pancreatitis; [[,]] bacteremia[[,]] including meningococcemia; [[,]] peritonitis; [[,]] bowel infection; [[,]] abdominal abscess; [[,]] ~~inflammation due to trauma, inflammation due to surgery~~; [[,]] chronic inflammatory disease; [[,]] ischemia; [[,]], ischemia-reperfusion injury of an organ or tissue; [[,]] tissue damage due to (i) disease, ~~tissue damage due to~~ (ii) chemotherapy or (iii) radiotherapy, or a ~~and~~ reaction[[s]] to an ingested, inhaled, infused, injected, or delivered substance; [[s,]] glomerulonephritis; [[,]] ~~bowel infection, an opportunistic~~

infection; ~~s, and for patients undergoing major surgery or~~ kidney failure and dialysis; ~~[[,]] immunosuppressive therapy; [[,]] patients who are immunocompromise~~~~[[d]]~~; ~~[[,]] patients on immunosuppressive agents, patients with HIV/AIDS; [[,]] patients with suspected endocarditis; [[,]] patients with fever, patients with fever of unknown origin, patients with cystic fibrosis; patients with diabetes mellitus; patients with chronic renal failure; patients with bronchiectasis; patients with chronic obstructive lung pulmonary disease (COPD); [[,]] chronic bronchitis; [[,]] emphysema; [[or]] asthma; patients with febrile neutropenia; patients with meningitis; patients with septic arthritis; patients with urinary tract infection; patients with necrotizing fasciitis, patients with other suspected Group A streptococcus infection, patients who have had a splenectomy; [[,]] patients with recurrent or suspected enterococcus infection; [[,]] other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococemia, post-pump syndrome; [[,]] cardiac stun syndrome; [[,]] myocardial infarction; [[,]] stroke; [[,]] congestive heart failure; [[,]] hepatitis; [[,]] cirrhosis; [[,]] epiglottitis; [[,]] E. coli 0157:H7, malaria, gas gangrene; [[,]] toxic shock syndrome; [[,]] mycobacterial tuberculosis; [[,]] *Pneumocystic carinii* pneumonia; [[,]] Leishmaniasis; [[,]] hemolytic uremic syndrome; [[,]] thrombotic thrombocytopenic purpura; [[,]] Dengue hemorrhagic fever; [[,]] pelvic inflammatory disease; [[,]] Legionella; [[,]] Lyme disease; [[,]] Influenza A; [[,]] Epstein-Barr virus; [[,]] encephalitis; [[,]] inflammatory diseases and autoimmunity and inflammation due to rheumatoid arthritis, osteoarthritis, or systemic lupus erythematosus; [[,]] inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis, hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis; an organ or tissue transplant~~[[s]]~~ and/or transplant rejection; including heart, liver, lung kidney bone marrow, graft-versus-host disease; transplant rejection, sickle cell anemia; [[,]] nephrotic syndrome; [[,]] or toxicity caused by monoclonal antibody of agents such as OKT3 or cytokine therapy, and cirrhosis.~~

15. *(currently amended)*: The method of claim any one of claims 1-14, wherein the inflammatory condition is SIRS.

16. *(currently amended)*: A method of identifying a polymorphism in a TLR-2 sequence that correlates with or is associated with prognosis of recovery from an inflammatory condition in a subject, the method comprising:

- (a) obtaining TLR-2 sequence information from a plurality group of subjects with an inflammatory condition;
- (b) based on the sequence information of (a), identifying at least one site of polymorphism ~~polymorphic nucleotide position~~ in the TLR-2 sequence in the subjects;
- (c) determining ~~[[a]]~~ genotypes defined by said at least one polymorphism at the polymorphic site for individual subjects ~~in the group~~;

- (d) determining recovery ability ~~capabilities~~ of individual subjects ~~in the group~~ from the inflammatory condition; and
- (e) correlating the genotypes determined in step (c) with the subjects' recovery ~~capabilities~~ determined in step (d),

thereby identifying said TLR-2 polymorphisms in said TLR-2 sequence ~~that correlate with recovery~~.

17. (*currently amended*): The method of claim 16, wherein the inflammatory condition is one that is due to, or associated with, selected from the group consisting of: Gram-positive, Gram-negative, culture-negative or fungal sepsis; septicemia; [[,]] septic shock; fever; bacterial viral, fungal or parasitic infection including Group A streptococcus infection; inflammation due to trauma, surgery or a medical or surgical condition associated with increased risk of infection or sepsis; [[,]] pneumonia; [[,]] septic shock, systemic inflammatory response syndrome (SIRS); [[,]] Acute Respiratory Distress Syndrome (ARDS); [[,]] acute lung injury; [[,]] infection, pancreatitis; [[,]] bacteremia; [[,]] including meningococcemia; [[,]] peritonitis; [[,]] bowel infection; [[,]] abdominal abscess; [[,]] inflammation due to trauma, inflammation due to surgery; [[,]] chronic inflammatory disease; [[,]] ischemia; [[,]] ischemia-reperfusion injury of an organ or tissue; [[,]] tissue damage due to (i) disease, tissue damage due to (ii) chemotherapy or (iii) radiotherapy, or a and-reaction[[s]] to an ingested, inhaled, infused, injected, or delivered substance; [[s,]] glomerulonephritis; [[,]] bowel infection, an opportunistic infection;s, and for patients undergoing major surgery or kidney failure and dialysis; [[,]] immunosuppressive therapy; [[,]] patients who are immunocompromise[[d]]; [[,]] patients on immunosuppressive agents, patients with HIV/AIDS; [[,]] patients with suspected endocarditis; [[,]] patients with fever, patients with fever of unknown origin, patients with cystic fibrosis; patients with diabetes mellitus; patients with chronic renal failure; patients with bronchiectasis; patients with chronic obstructive lung pulmonary disease (COPD); [[,]] chronic bronchitis; [[,]] emphysema; [[or]] asthma; patients with febrile neutropenia; patients with meningitis; patients with septic arthritis; patients with urinary tract infection; patients with necrotizing fasciitis, patients with other suspected Group A streptococcus infection, patients who have had a splenectomy; [[,]] patients with recurrent or suspected enterococcus infection; [[,]] other medical and surgical conditions associated with increased risk of infection, Gram positive sepsis, Gram negative sepsis, culture negative sepsis, fungal sepsis, meningococcemia, post-pump syndrome; [[,]] cardiac stun syndrome; [[,]] myocardial infarction; [[,]] stroke; [[,]] congestive heart failure; [[,]] hepatitis; [[,]] cirrhosis; [[,]] epiglottitis; [[,]] E. coli 0157:H7, malaria, gas gangrene; [[,]] toxic shock syndrome; [[,]] mycobacterial tuberculosis; [[,]] *Pneumocystis carinii* pneumonia; [[,]] Leishmaniasis; [[,]] hemolytic uremic syndrome; [[,]] thrombotic thrombocytopenic purpura; [[,]] Dengue hemorrhagic fever; [[,]] pelvic inflammatory disease; [[,]] Legionella; [[,]] Lyme disease; [[,]] Influenza A; [[,]] Epstein-Barr virus; [[,]] encephalitis; [[,]] inflammatory diseases and autoimmunity and inflammation due to rheumatoid arthritis, osteoarthritis or systemic lupus erythematosus; [[,]] inflammatory bowel disease, idiopathic pulmonary fibrosis, sarcoidosis,

hypersensitivity pneumonitis, systemic vasculitis, Wegener's granulomatosis; an organ or tissue transplant[[s]] and/or transplant rejection; ~~including heart, liver, lung kidney bone marrow, graft-versus-host disease;~~ ~~transplant rejection~~; sickle cell anemia; [[,]] nephrotic syndrome; [[,]] or toxicity caused by monoclonal antibody of agents such as OKT3 or cytokine therapy, and ~~erithrosis.~~

18. *(currently amended)*: A kit useful for determining a genotype of a subject or subjects at a defined polymorphic nucleotide position within a polymorphic site in a TLR-sequence from the subject or subjects, ~~wherein knowledge of the~~ which genotype is associated with ~~provides a~~ prognosis of the subject's ability to recover from an inflammatory condition, the kit comprising;

- (a) a restriction enzyme with specificity that distinguishes ~~capable of distinguishing~~ alternate nucleotides at the polymorphic site or sites; or
- (b) a labeled oligonucleotide having sufficient complementarity ~~that is sufficiently complementary~~ to an alternate nucleotide sequence at the polymorphic site such that the oligonucleotide hybridizes in a distinguishable manner to a sequence that comprises ~~so as to be capable of specifically hybridizing to said alternate nucleotide sequence, thereby permitting determination of~~ ~~whereby the genotype at~~ ~~[[of]] the polymorphic site may be determined~~; and
- (c) optionally, instructions for use of said enzyme and/or said oligonucleotides in determining the genotype.

19. *(currently amended)*: The kit of claim 18, wherein the polymorphic ~~a polymorphism~~ site is at ~~corresponds to~~ nucleotide position 201 of SEQ ID No.1.

20. *(currently amended)*: The kit of claim 18 ~~or 19~~ further comprising an oligonucleotide primer or a set of oligonucleotides suitable to amplify a region flanking ~~including~~ the polymorphic site.

21. *(currently amended)*: The kit of claim 20, further comprising a polymerizing polymerization agent that promotes or permits nucleotide polymerization.

22. *(currently amended)*: A method for identifying ~~selecting a group of subjects as being~~ suitable for a trial that tests ~~for determining the efficacy of a candidate drug known to be, or~~ suspected of being, useful for treating ~~the treatment of~~ an inflammatory disease or condition, the method comprising

- (a) determining a genotype defined by ~~for one or more polymorphic sites in the~~ TLR-2 sequence for each of said subjects, wherein said genotype is indicative of

the subject's recovery ability to recover from the inflammatory disease or condition, and

(b) sorting subjects into a suitable and unsuitable group for said trial based on the[[ii]]
subjects' genotype.

23. *(currently amended)*: A The method for testing a candidate drug for its efficacy in the treatment of an inflammatory disease or condition wherein said disease or condition is associated with a genotype defined by a polymorphism in a TLR-2 gene, comprising:

(a) identifying subjects that are suitable for a trial that tests said candidate drug in accordance with of claim 22 further comprising; and

(b) administering the candidate drug to [[the]] each of said subjects or a subset of subjects, and determining comparing each subject's the subjects' ability to recover from the inflammatory condition responses to said candidate drug in comparison with the subjects' genotype,

thereby testing said candidate drug.

24. *(currently amended)*: The method of claim 23, wherein a further comprising comparing subject's response to the candidate drug is measured as the ability to recover from the inflammatory condition based on genotype of the subject.

25. *(currently amended)*: The [[A]] method of claim 22 wherein the inflammatory disease or condition is associated with for selecting a group of subjects for determining the efficacy of a candidate drug known or suspected of being useful for the treatment of a gram positive infection; the method comprising determining a genotype for one or more polymorphic sites in the TLR-2 sequence for each subject, wherein said genotype is indicative of the subject's likelihood of developing a gram positive infection and sorting subjects based on their genotype.

26. *(currently amended)*: The method of claim 23 [[25]] wherein the inflammatory disease or condition is associated with further comprising, administering the candidate drug to the subjects or a subset of subjects and determining each subject's ability to recover from the a gram positive infection.

27. *(currently amended)*: The method of claim 24 [[26]], wherein the inflammatory disease or condition is associated with a gram positive infection further comprising comparing subject response to the candidate drug based on genotype of the subject.

CANCEL Claims 28-39

40. ***(currently amended):*** The [[A]] method of claim 1 wherein the inflammatory condition is a result of ~~for determining a risk of developing a gram positive infection in a subject, the method comprising determining a genotype of said subject at a polymorphic site in the subject's toll like receptor 2 (TLR-2) sequence, wherein if said genotype is a risk genotype, it is indicative of the subject's risk of gram positive infection.~~

41. **(original):** The method of claim 40, wherein the polymorphic site is at position 201 of
 SEQ ID NO:1.

42. **(currently amended):** The method ~~any one of claim 40~~ claims 40-41, further comprising ~~ascertaining~~ determining the TLR-2 gene sequence information ~~for~~ of the subject.

43. **(currently amended):** The method ~~any one of claim 40, claims 40-42,~~ wherein said determining of genotype determination is performed on a nucleic acid sample from the subject.

44. **(currently amended):** The method of claim 43, further comprising the step of obtaining
[[a]] the nucleic acid sample from the subject ~~patient~~.

45. **(currently amended):** The method ~~any one of claim 40 claims 40-44~~, wherein said ~~determining of genotype is determined by comprises one or more of the following techniques:~~

- (a) restriction fragment length analysis;
- (b) sequencing;
- (c) hybridization;
- (d) oligonucleotide ligation assay;
- (e) ligation rolling circle amplification;
- (f) 5' nuclease assay;
- (g) polymerase proofreading methods;
- (h) allele specific PCR; and
- (i) reading sequence data.

46. **(currently amended):** The method of claim 40 ~~any one of claims 40-45~~, wherein the risk genotype of the subject is predictive or indicative of the ~~the~~ [[a]] subject's risk of developing a gram positive infection.

47. **(original)**: The method of claim 46, wherein the risk genotype has at least one A nucleotide at position 201 of SEQ ID NO: 1.

48. *(currently amended)*: The method of claim 46, wherein the protective genotype is defined as homozygosity ~~homozygous~~ for T at position 201 of SEQ ID NO:1.

Cancel claims 49-51

52. *(currently amended)*: An array of nucleic acid molecules immobilized ~~attached~~ to a solid support, the array comprising:

- (a) [[an]] a first set of oligonucleotides that
 - (i) [[will]] hybridize to a nucleic acid molecule consisting of SEQ ID NO:1 in which ~~wherein~~ the nucleotide at position 201 is A, under conditions wherein ~~in which~~
 - (ii) the oligonucleotides of the first set [[will]] do not substantially hybridize to a nucleic acid molecule consisting of SEQ ID NO:1 in which ~~wherein~~ the nucleotide at position 201 is T; and/or
- (b) [[an]] a second set of oligonucleotides that
 - (i) [[will]] hybridize to a nucleic acid molecule consisting of SEQ ID NO: 1, in which ~~wherein~~ the nucleotide at position 201 is T, under conditions wherein ~~in which~~
 - (ii) the oligonucleotides of the second set will not substantially hybridize to a nucleic acid molecule consisting of SEQ ID NO: 1 in which ~~wherein~~ the nucleotide at position 201 is A.

Cancel Claims 53-55